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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/642,440	08/14/2003	Eli Wallace	064804-0054	2454

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/642,440	WALLACE ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 25-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 25-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL ACTION

Applicant's amendment of 8-10-06 has been fully considered. Applicant's argument has overcome items (e), (f) and (g) of the previous 112/2nd rejection. However, said argument has not overcome items (a)-(d) of said rejection as well as the rejection of Provisional Obviousness-type Double Patenting. Thus, said rejections are maintained. In view of the broad compound scope, the following new ground of rejection is presented.

Claims 13-24 have been withdrawn.

Claims 1-12 and 25-36 are pending.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Lack of Written Description:** Claims 1-12 and 25-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "solvates" does not have adequate description. The specification defines a "solvate" as "an aggregate of a

molecule with one or more solvent mlecules. However, it does not provides guidance for selecting solvents, nor does it provide specific ratio necessary to form a solvate.

2. **Scope of Enablement:** Claims 1-3, 5, 7-12, 25-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the make and use of compounds of formula I wherein R^2 is *H, or a substituted or unsubstituted C_{1-8} alkyl group*, does not reasonably provide enablement for the make and use of compounds of formula I wherein R^2 is *C_{1-8} alkyl having a terminal carbon atom bound to one of the ring atoms of R^1* . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 1 recites a compound of formula I having

substituents of $-NR^1R^2$, A and R^3. Variable R^2 represents H, a substituted or unsubstituted C_{1-8} alkyl group, or C_{1-8} alkyl having a terminal carbon atom bound to one of the ring atoms of R^1. The limitation of C_{1-8} alkyl having a terminal carbon atom bound to one of the ring atoms of R^1 suggests either a polycyclic system or a spiro-cycle formed by R^1 and R^2. Such a ring system renders the claim unduly broad.

Claims 2, 3, 5, 7-12, 25-35 are either directly or indirectly dependent on claim 1, and thus carry over the same unduly broad scope.

The amount of direction or guidance presented: Regarding the preparation of compounds of formula I, the specification only provides the starting material for R^1 as a *phenyl* group and R^2 as *phenoxy* or *benzyloxy*. The specification is silent as to the availability of necessary reactants needed to prepare a compound of formula I with R^2 forming a ring with R^1. Note, **In re Howarth** 210 USPQ 689; **Ex parte Moersch** 104 USPQ 122, for the need to show starting material sources commensurate with the claims' scope.

Regarding the biological activity, the specification only details the method of EGFR/ErbB2 Enzymatic Assay without specifying which compounds have been tested. The specification only generally indicates that compounds of the present invention have IC_{50} from less than 1nM to 50mM. However, the tested compounds do not have the substituent of R^2 bound to one of the ring atoms of R^1. Due to the structural differences, the activity of the tested compounds cannot be extrapolated to other compounds of formula I wherein the substituent of R^2 bound to one of the ring atoms of R^1 (or forming a ring).

Thus, the specification does not provide sufficient enablement commensurate with the broad Markush group of formula I.

The state of the prior art: Typically, quinazoline compounds are known to treat solid tumor, rheumatoid arthritis or infections as evident by **Stogniew et. al.** (US 6,017,922 B1 – cited previously). However, Stogniew's compounds do not have a substituent such as R^2 forming a ring with R^1. Thus, the state of the prior art does not provide adequate enablement for making compounds in commensurate with the scope of formula I.

The relative skill of those in the art: Even with the advanced training, the skilled medicinal chemist and/or clinician would have to carry out extensive research to make an array of compounds of formula I, and select an effective compound from such a large Markush group for antiangiogenic, and vascular permeability reducing effect. Not only one has to determine the inhibitory activity on EGFR/ErbB2, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula I, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification does not provide starting materials for making compounds of formula I with various ring systems formed by R^1 and R^2. It also fails to provide biological data for using the claimed compounds in a method of treating cancers. Thus, with the large Markush group of formula I, without the guidance for starting material sources of rings formed by R^1 and

R^2, undue experimentation is necessary for making such an array of compounds as well as establishing biological activity for those compounds as inhibitors of EGFR/ErbB2.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-12 and 25-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Variable R^6 appears in many places which makes it hard to determine the intended scope for many of the claims. Besides, when R^4 and R^6, or R^6 and R^8 form a ring which can be substituted with groups having R^6, it is unclear what the intended scope for R^6 is.

Likewise, when R^8 and R^9 form a ring which can be substituted with groups having R^8, it is unclear what the intended scope for R^8 is.

b. It is unclear how Z is bonded to U. It appears that Z is bonded to U via the N or =N-.

c. Claim 26 lacks antecedent basis because it depends on claim 7 but recite R^6 to be an "optionally substituted alkyl or cycloalkyl" while claim 1 requires R^6 of Z to be –NH when W is inter alia O.

d. Claims 27-30 also lack antecedent basis as being dependent on claim 26.

e. Claims 32-35 lack antecedent basis because claim 32 depends on claim 1 but recite R^6 to be an "optionally substituted alkyl or cycloalkyl" while claim 1 requires R^6 of Z to be –NH when W is inter alia O, NR^6, S, SO or SO_2.

f. Claim 36 lacks antecedent basis because it depends on claim 1 but recites species that are outside the scope of claim 1.

Double Patenting

The **nonstatutory double patenting** rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-12 and 25-36 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 10, 20-91 and 101-106

of copending Application No. 10/914,974 (Pregrant Publication No. US 2005/0043334 A1 or PP'334). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed formula I overlaps with formula I of PP'334 when their variables represent the following:

i. A is Z (or $-(U)_nZ$; n = 0);

ii. X is N;

iii. R^1 is a substituted or unsubstituted, monocyclic or bicyclic, aryl moiety;

iv. R^2 is H or a substituted or unsubstituted C_{1-8} alkyl;

v. Z is the 5-membered ring having N, V and W single/double bonded to N;

vi. V is CR^7R^8 or CR^8R^9.

Species in claims 101-106 of PP'334 also anticipate the instantly claimed formula I, and are analogous to some species recited in the instant claim 36. Species in the instant claim 36 also anticipate formula I of PP'334.

Thus, it would have been within the level of the skilled chemist to select compounds of the instant formula I in view of formula I claimed in PP'334.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Note, applicant's argument and the amended claims have not overcome the above ODP rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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1-7-07

Tamthom N. Truong
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Art Unit 1624

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